REMARKS

Favorable reconsideration of the subject application is respectfully requested in view of the above amendments and the following remarks. By the present amendment, claims 18 and 21 are canceled. In addition, claim 17 is amended to more specifically recite certain aspects of the present invention. Support for these amendments is provided throughout the specification and claims as originally filed. Accordingly, these amendments do not constitute new matter.

Rejection Under 35 U.S.C. § 103(a) over Young

Claims 7-14 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Young. The Examiner asserts that Young teaches liposomal drug formulations comprising empty liposomes, but concedes that Young fails to teach the claimed neoplastic agents, namely camptothecins and vinca alkaloids. However, the Examiner submits that Young teaches that empty liposomes influence the drug release rate, and concludes would be obvious to one of skill in the art that this would apply to any drug, including camptothecins and vinca alkaloids.

Applicants respectfully traverse this basis of rejection and submit that the Examiner has failed to establish a prima facie case of obviousness over Young. To establish a prima facie case of obviousness, the following three criteria must be met: (1) the prior art must teach or suggest all of the claim limitations; (2) there must be some suggestion or motivation, either in the references or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine the reference teachings; and (3) there must be a reasonable expectation of success. M.P.E.P., 8th Ed. § 2143. Applicants submit that Young fails to provide the required motivation to alter the teachings of Young to achieve the claimed compositions, and also fails to establish any reasonable expectation of success. Thus, Young fails to render the present invention obvious. Applicants can only conclude that the Examiner is applying impermissible hindsight, based upon the teachings of the instant application, in drawing his conclusion that the presently claimed invention is obvious over Young.

In summary, Applicants submit that Young provides no motivation to include empty liposomes in liposomal drug formulations comprising camptothecins or vinca alkaloids, as presently claimed. The teachings of Young are limited to the use of empty liposomes in liposomal drug formulations that are administered subcutaneously (SC) or intramuscularly (IM). Since camptothecins and vinca alkaloids are not administered SC or IM, the skilled artisan would not be motivated by Young to include empty liposomes in liposomal drug formulations comprising either camptothecins or vinca alkaloids. Furthermore, the skilled artisan would have no reasonable expectation that the use of empty liposomes in liposomal formulations comprising camptothecins or vinca alkaloids would have any benefit, based upon Young's teaching that the inclusion of empty liposomes effects liposome stability at a local site of injection, which, of course, is irrelevant to intravenous delivery.

As described in the instant specification, the presently claimed invention is based on Applicants' surprising discovery that including empty liposomes in intravenously administered liposomal drug formulations increases the half-life of a drug in the bloodstream. In general, liposomes are cleared from the bloodstream by cells of the reticuloendothelial system (RES). Typically, the RES will remove 80-95% of a dose of injected liposomes within one hour, effectively out-competing a selected target site for uptake of the liposomes. Applicants discovered that by including empty liposomes, it is possible to effectively shield liposomes containing drug from the RES. The empty liposomes actually extend the blood circulation lifetime of the liposomes containing drug by acting as "decoys." In essence, the empty liposomes keep the RES busy and, as a result, the serum half-life of the liposomes containing drug is increased.

Clearly, nothing taught or described in Young would motivate the skilled artisan to add empty liposomes to liposomal drug formulations for intravenous administration. Indeed, Young states unequivocally that the field of the invention is only relevant to IM or SC delivery. "The field of this invention, i.e., intramuscular or subcutaneous delivery of liposomal [sic] drug is not applicable and cannot be compared to the intravenous route of administration since the mechanism of drug release by the intramuscular route is entirely different, i.e. the liposomes are

destabilized at the intramuscular or subcutaneous injection site thereby releasing the drug..." (column 3, line 67 to column 4, line 6).

Further insight into why Young's teachings are only applicable to SC or IM administration is provided under the section titled "B. Release Characteristics of Lipids and Encapsulated Compound" (column 17, line 3 to column 18, line 42). For example, Young states that "[t]he latter results indicate that lipid clearance is governed by bulk effects related to average liposome sizes, and forms the basis, according to one aspect of the invention, of controlling release characteristics of smaller liposomes by the addition of larger, empty ones" (column 17, lines 52-57). And later, Young states "[t]his finding suggests that liposomes are destabilized and release their encapsulated contents predominantly at the site of injection, with lipid clearance from the site being handled by a different, slower mechanism" (column 17, line 68 to column 18, line 4). These statements indicate that bulk effects at the site of IM or SC injection influence the rate of destabilization of drug-loaded liposomes. Clearly, such bulk effects at a tissue site are not relevant for comparison to the fate of IV administered liposomes. In the case of IV administered liposomes, clearance from the plasma compartment predominantly reflects removal of drug-loaded liposomes by the RES. This mechanism is entirely distinct from those implicated by Young. Accordingly, the skilled artisan would have no expectation from the information provided in Young that the addition of empty liposomes to liposomal drug formulations would influence plasma pharmacokinetics following IV administration. To the contrary, the effect of empty liposomes on clearance of intravenously administered liposomal drugs was only first discovered and described by Applicants, in the instant application.

In the Office Action, the Examiner indicates that he disagrees with Applicants' statement that camptothecins and vinca alkaloids are not administered SC or IM. Applicants strongly disagree with the Examiner's position and submit that it is known in the art that camptothecins and vinca alkaloids are not administered either SC or IM. For the Examiner's convenience, Applicants have enclosed copies of the package inserts for FDA-approved formulations of various camptothecins and vinca alkaloids, including topotecan, irinotecan, vincristine, and vinorelbine. All state that the drug is for intravenous administration only and

many comment as to the dangers from extravasation or injection at sites other than intravenous. In addition, Applicants submit a Declaration of Dr. James H. Goldie, an experienced clinical oncologist and former Head of the Division of Medical Oncology at the University of British Columbia, attesting to the fact that camptothecins and vinca alkaloids are not administered either SC or IM.

As described in Dr. Goldie's declaration, free camptothecins and vinca alkaloids are not administered by SC or IM routes because they are cytotoxic agents and the high drug concentrations that result from such local administration can cause severe inflammation and/or necrosis. Furthermore, while liposome encapsulation may ameliorate some of this local toxicity, as suggested for vincristine (Boman et al., 1996, Cancer Chemotherapy and Pharmacology 37: 351-355), SC or IM administration of a liposomal camptothecin or vinca alkaloid would still not be contemplated by the skilled artisan for a variety of reasons. Chemotherapy, with agents such as camptothecins and vinca alkaloids, is used in the treatment of disseminated (metastatic) disease or in patients for whom metastasis cannot be excluded; localized cancer is removed surgically or treated with radiation therapy. Accordingly chemotherapeutic agents are intended to be delivered systemically to ensure access to all possible tumor sites within the body. Liposomal encapsulation allows preferentially drug delivery to tumor sites as a result of liposome extravasation from the blood compartment via leaky tumor blood vessels. Liposomal drugs are therefore administered directly to the blood by IV or intra-arterially administration.

For liposomal chemotherapeutic agents, such as camptothecins and vinca alkaloids, the SC route would be understood by the skilled artisan to be unsuitable, because only a small proportion of the administered liposomes are able to reach the blood compartment and subsequently access tumor sites. For example, Allen et al., 1993 (Biochimica et Biophysica Acta, 1150: 9-16) compared blood and tissue liposome levels following SC, IV or intraperitoneal (IP) administration. These authors showed that liposomes of 110-120 nm diameter or larger were unable to access the blood compartment following SC administration (<1% of injected dose) (see Figure 3, Allen et al.). Even small liposomes (80-90 nm), when administered by SC injection, achieved only about 30% of the maximum blood levels seen following IV

administration, and this modest bioavailability was dependent on the presence of PEG-lipid. Although Allen et al. did not specifically evaluate IM injection, this route is understood in the art to be similar to SC administration, in that it requires migration of the liposomes via the lymphatic system to lymph nodes and subsequent drainage to the blood compartment. Accordingly, similar reductions in liposome bioavailability would be expected for the IM route. In view of the fact that liposomes are intended to increase drug delivery to tumor sites, it would not be logical to administer such formulations by the SC route, knowing that this would result in decreased tumor drug levels, because only a minor proportion of the administered liposomes would reach the blood compartment, from which access to tumor sites is achieved. Thus, Applicants submit that the skilled artisan would not be motivated by any of the references cited by the Examiner, alone or in combination, to administer liposomal camptothecin or vinca alkaloid formulations SC or IM.

Further regarding the references cited by the Examiner as supporting his position that camptothecins and vinca alkaloids may be administered SC or IM, Applicants note that none of these references demonstrate successful SC or IM delivery of camptothecins or vinca alkaloids. Rather, they are patent documents that merely describe, in general, various potential routes of delivery that might be appropriate for any of a large number of different drugs. Applicants submit that, even in light of these references, the skilled artisan would still understand that camptothecins and vinca alkaoids are not administered either SC or IM and would, therefore, not be motivated to apply the teachings of Young regarding SC and IM drug delivery to liposomal formulations comprising drugs that are not administered either SC or IM, such as camptothecins and vinca alkaloids.

In light of these remarks, Applicants submit that the claimed invention is clearly not obvious over Young, and respectfully request that the Examiner reconsider and withdrawn this basis of rejection.

Rejection Under 35 U.S.C. § 103(a) over WO 91/04019

Claims 7-13 and 21 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over WO 91/04019. The Examiner asserts that WO 91/04019 teaches liposomal drug compositions comprising empty liposomes, including liposomes comprising sphingomyelin and cholesterol. The Examiner concedes that WO 91/04019 fails to teach the claimed neoplastic agents and the claimed sphingomyelin to cholesterol ratios. However, the Examiner submits that WO 91/04019 teaches that empty liposomes increase drug bioavailability, and it would be obvious to one of skill in the art that this would apply to any drug. In addition, the Examiner asserts that it would be obvious to vary the sphingomyelin:CHOL ratios to achieve the claimed ratios.

Applicants traverse this basis of rejection and submit that the Examiner has failed to establish a prima facie case of obviousness over WO 91/04019. Applicants submit that the teachings of WO 91/04019 would provide the skilled artisan no motivation, or reasonable expectation of success, to include empty liposome in liposomal formulations of drugs that are administered intravenously, such as the presently claimed camptothecins and vinca alkaloids (claims 7-13), since, like Young, discussed above, WO 91/04019 is directed to methods and compositions for prolonging the bioavailability of therapeutic peptides or proteins after SC or IM administration. Furthermore, Applicants submit that WO 91/04019 fails to teach each feature recited in claim 21, including the feature that the liposomes comprise sphingomyelin and cholesterol at a molar ratio from 75/25 mol%/mol% sphingomyelin/cholesterol to 30/50 mol%/mol% sphingomyelin/cholesterol.

Regarding claims 7-13, Applicants submit that upon careful review of the entirety of WO 91/04019, the skilled artisan would understand that its teachings related to the use of empty liposomes are limited to SC and IM administration. For example, WO 91/04019 explicitly states that "[t]he liposomes of the present invention are believed to prolong bioavailability by providing a vesicle which has sufficient structural integrity and characteristics which resist dissolution at the point of injection and in lymphatic system, while at the same time

being amenable to gradual release of the encapsulated peptide or protein in the blood stream. Further, the lipid vesicles containing the therapeutic peptide or protein are not so stable that they are taken up and consumed by macrophages prior to release of the therapeutic agent" (page 4, line 32 to page 5, line 6). WO 91/04019 further states that "the liposome must be composed of suitable lipids such that it is relatively stable in lymph, but releases its contents readily in serum or plasma" (page 4, lines 21-24). Accordingly, Applicants submit that, based upon the teaching of WO 91/04019, the skilled artisan would understand that empty liposomes effect the dissolution of liposomes containing drug at the SC or IM delivery site, as well as in the lymphatic system. This, of course, is irrelevant to liposomal drug compositions that are delivered intravenously, such as those comprising camptothecins and vinca alkaloids. And, as discussed at length above in reference to the Section 103 rejection based upon Young, it is understood in the art that liposomal camptothecin and vinca alkaloid formulations would not be administered either SC or IM. Accordingly, the teachings of WO 91/04019 would not motivate the skilled artisan to add empty liposomes to liposomal compositions comprising camptothecins and vinca alkaloids, which are administered intravenously.

Applicants further emphasize that the liposomal compositions of WO 91/04019 are described as being unstable in serum, such that they release their encapsulated drug before being taken up by the RES. Applicants submit that given this very rapid release of drug, the skilled artisan would not be motivated to use these compositions for intravenously administered liposomal drug compositions, wherein there is clearly a desire to extend the circulation lifetime of drug-containing liposomes in the blood, so that they are in circulation long enough to ensure their delivery to the diseased cell or tissue, e.g., via extravasation. This desire is understood in the art and made clear in the instant application, wherein it is precisely because drug-loaded liposomes injected intravenously are taken up by macrophages that the addition of empty liposomes can increase their circulation lifetime in the blood.

With respect to claim 21, Applicants submit that WO 91/04019 actually teaches away from the claimed SM:CHOL ratios. The liposomes described in this reference must be unstable in order to release drug, via disruption or dissolution of the liposome bilayer. In

numerous passages, this reference teaches that liposomes comprising more than 10 mol percent cholesterol do not provide any advantage in enhancing bioavailability of the drug.

WO 91/04019 is directed to liposomal formulations of therapeutic peptides or proteins that, being hydrophilic molecules, are not able to permeate across the liposomal membrane. Release of these agents from the liposomes described in WO 91/04019 involves disruption or dissolution of the liposomal bilayer (e.g., page 1, lines 33-35). This requirement that the liposomes be relatively unstable in serum or plasma is explicitly addressed by limiting the cholesterol content to less than 10 mole percent (page 4, lines 25-27; page 9, lines 10-11; and page 17, lines 10-16). In Example 6 (page 17, lines 3-16), WO 91/04019 describes liposomes comprising 10 mole% cholesterol and containing human calcitonin (hCT). It is stated that "when cholesterol is present in 10 mole% in the lipid bilayer of single lamellar vesicles which are otherwise effective in prolonging the biological effect of hCT [.....], the biological effect of hCT to lower serum calcium is abolished." The inclusion of cholesterol at 10 mole% presumably prevents liposome disruption and release of the protein or peptide. Accordingly, WO 91/04019 states, in the same paragraph, "[l]iposomes containing more than 10 mole% cholesterol are therefore not a preferred dosage form," and more explicitly in the Detailed Description of the Invention (page 9, lines 10-11), "[c]holesterol must comprise less than 10 mole percent if used in the preparations." Therefore, Applicants submit that WO 91/04019 provides absolutely no motivation to use the SM:CHOL ratios recited in claim 21. However, without acquiescence to this basis of rejection, Applicants note that claim 21 is canceled by the present amendment, thereby obviating this aspect of the present rejection.

Furthermore, Applicants note that the liposome formulations described in both Young and WO 91/04019 are relatively large liposomes, based on information provided in the Examples of each reference. Specifically, WO 91/04019 describes the preparation of liposomes by extrusion through 200 nm pore size filters. Similarly Young describes the preparation of liposomes by extrusion through various pore size filters from 200 nm to 1 micron. The resulting liposomes were of similar size to the filter pore size (see Table 3 in Young). Accordingly while Young and WO 91/04019 only exemplify liposomes of about 150-200 nm diameter or greater.

In view of Allen, therefore, which indicates that liposomes of this size are not cleared from the site of administration, it would be understood by someone of ordinary skill in the art that the liposome formulations described by Young and WO 91/04019 were not cleared from the site of administration (SC or IM) and that peptide, protein or drug levels observed in the blood over time reflected encapsulated contents that had been released from liposomes remaining at the injection site. Accordingly, any effect of empty liposomes would be understood to result from interactions occurring at the SC or IM injection site, and there would be no basis to conclude that this effect could be extrapolated to the situation wherein drug-loaded liposomes were administered intravenously in combination with empty liposomes. Again, these references provide absolutely no motivation for the skilled artisan to include empty liposomes in liposomal formulations comprising drugs such as camptothecins and vinca alkaloids, which are administered systemically, e.g., intravenously.

In light of the above remarks and amendment, Applicants submit that the Examiner has failed to establish the requisite motivation to modify the teachings of either Young or WO 91/04019 to achieve the presently claimed invention and, therefore, respectfully requests that the Examiner reconsider and withdraw this basis of rejection.

Rejection Under 35 U.S.C. § 103(a) over Kirpotin (6,110,491) in combination with either Young or WO 91/04019

All pending claims stand rejected over Kirpotin in combination with either Young or WO 91/04019. Essentially, the Examiner asserts that Kirpotin teaches liposomes comprising precipitated drug, while Young and WO 91/04019 teach liposomal formulations comprising empty liposomes. The Examiner concludes that the skilled artisan would be motivated to include empty liposomes in the formulations described by Kirpotin, in order to benefit from increased bioavailability or slower drug release, as allegedly described in Young and WO 91/04019.

Applicants respectfully traverse this basis of rejection and submit that the cited references, alone or in any combination, do not render the claimed invention obvious. Applicants submit that the presently claimed invention is both novel and nonobvious over the cited references.

With regard to claims 7-13 and 23-29, Applicants note that these claims are directed to liposomal compositions comprising either camptothecins or vinca alkaloids. Applicants respectfully submit, for reasons detailed above, that neither Young nor WO 91/04019 teaches the use of empty liposomes in formulations for intravenous delivery. Accordingly, since camptothecins and vinca alkaloids are administered exclusively intravenously, the skilled artisan would have no motivation to include empty liposomes, as taught by either Young or WO 91/04019, in liposomal formulations comprising camptothecins or vinca alkaloids, including any that might be described in Kirpotin. Clearly, Kirpotin fails to remedy this deficiency, as it does not teach the use of empty liposomes at all, much less in formulations comprising camptothecins or vinca alkaloids. Accordingly, Applicants submit that these references, alone or in any combination, fail to render obvious claims 7-13 and 23-29.

With regard to claims 17, and claim 22 dependent therefrom, Applicants submit that these claims are drawn to a particular embodiment of the present invention, which possesses surprising advantages over the prior art, and which is not obvious over the cited combinations of references. Applicants note that the present invention is based on the surprising discovery that the inclusion of empty liposomes in formulations comprising drug-loaded liposomes protects the drug-loaded liposomes from RES uptake, thereby extending the duration of time that the drug-loaded liposomes are present in the circulation. The mechanism by which empty liposomes exert this effect is understood to be by at least partially saturating the RES system with empty liposomes, thereby blocking their ability to take up drug-loaded liposomes. Accordingly, the present invention offers particular advantages to liposomal drug formulations having a high drug to lipid ratio, such that a relatively low number of liposomes need be administered in order to deliver the appropriate amount of drug. These high drug to lipid ratio liposomes are rapidly removed from the bloodstream by the RES, given that there is a reduced number of such liposomes in circulation. The addition of empty liposomes ties up the RES system, allowing more drug-loaded liposomes to circulate in the bloodstream for a time sufficient to ensure that they are able to reach target disease tissues. The fundamental and surprising discovery that liposomal formulations comprising drug-loaded liposomes with high drug to lipid ratios in combination with empty liposomes offer multiple advantages over previous liposomal drug

formulations is a surprising discovery of the present invention. As described in the instant specification, high drug to lipid ratio liposomes comprising precipitated drug release drug more slowly than liposomes comprising only free drug, and empty liposomes reduce the rate at which these liposomes are cleared from the circulation by the RES. Thus, liposomes having both these features provide sustained drug delivery over a longer period of time than comparable formulations lacking these features. Furthermore, these advantages are not limited to liposomes having any particular lipid composition, since RES uptake of liposomes is largely non-specific with regard to liposome composition. Accordingly, the presently claimed invention possesses surprisingly superior properties over the prior art. The features of the presently claimed invention were not previously combined, and the advantages associated with the claimed combination of features were previously unrecognized.

Applicants further note that U.S. patent law clearly establishes that the mere fact that the teachings of the prior art can be combined or modified, or that a person having ordinary skill in the art is capable of combining or modifying the teachings of the prior art, does not make the resultant combination prima facie obvious, as the prior art must also suggest the desirability of the combination (see, e.g., In re Mills, 16 USPQ2d 1430 (Fed. Cir. 1990); In re Fritch, 23 USPQ2d 1780 (Fed. Cir. 1992)). Since none of the cited references teach or suggest any advantage or desirability of modifying the teachings of the references to produce the claimed liposomal compositions comprising both precipitated drug and empty liposomes, Applicants submit that the Examiner has failed to establish a prima facie case of obviousness and respectfully request that this basis of rejection be withdrawn.

Rejection Under 35 U.S.C. § 103(a) over WO 99/13816 in combination with either Young or WO 91/04019

All pending claims stand rejected over WO 99/13816 in combination with either Young or WO 91/04019. Specifically, the Examiner alleges that WO 99/13816 teaches liposomal formulations comprising camptothecins in precipitated form, while Young and WO 91/04019 teach liposomal formulations comprising empty liposomes. The Examiner concludes that the skilled artisan would be motivated to include empty liposomes in the formulations

described by WO 99/13816, in order to benefit from increased bioavailability or slower drug release, as described in Young and WO 91/04019.

Applicants respectfully traverse this basis of rejection and submit that the cited references, alone or in any combination, do not render the claimed invention obvious.

With regard to claims 7-13 and 23-29, Applicants note that these claim recite the feature that the active agent is a camptothecin or vinca alkaloid. Applicants respectfully submit, for the reasons detailed above, that neither Young nor WO 91/04019 teaches the use of empty liposomes in formulations for intravenous delivery. Accordingly, since camptothecins and vinca alkaloids are administered exclusively intravenously, the skilled artisan would have no motivation to include empty liposomes, as taught by either Young or WO 91/04019, in liposomal formulations comprising camptothecins or vinca alkaloids. Clearly, WO 99/13816 fails to remedy this deficiency, as it does not teach the use of empty liposomes at all, much less in formulations comprising camptothecins or vinca alkaloids. Accordingly, Applicants submit that these references, alone or in any combination, fail to render obvious claims 7-13 and 23-29.

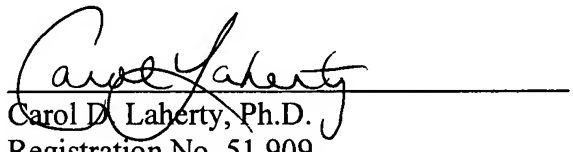
Regarding claims 17 and 22, Applicants submit that these claims are not obvious in light of the cited combinations of references, for the same reasons that these claims are not obvious over the previously applied combination of references. The instant claims are drawn to a liposomal drug formulation comprising both liposomes loaded with precipitated drug and empty liposomes, which combination of features provides surprising advantages over the art. While the prior art references may individually recite one of the features of the present claimed invention, none of these references recite the particular combination of references or provide any suggestion to combine any of the references to achieve the claimed invention, nor any recognition that such a combination would possess the surprising properties only first described in the instant application. Applicants submit that both rejections based upon the combinations of references can only be made based upon the teachings of the instant application and, therefore, clearly rely on impermissible hindsight. Accordingly, Applicants respectfully request that this basis of rejection be withdrawn.

As a final consideration, Applicants submit that, assuming arguendo, any cited reference or combination of references was considered sufficient to entice the skilled artisan to attempt to modify or combine features of prior art liposomal compositions, this would amount to "obvious to try," which is clearly below the legal threshold required to establish obviousness. In re O'Farrell, 853 F.2d 894, 903, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988).

Applicants respectfully submit that all of the claims remaining in the application are allowable. Favorable consideration and a Notice of Allowance are earnestly solicited.

Respectfully submitted,

SEED Intellectual Property Law Group PLLC



Carol D. Laherty, Ph.D.
Registration No. 51,909

CDL:teb
Enclosure:
Postcard
Copies of Package Inserts for FDA-approved formulations of various camptothecins and vinca alkaloids

701 Fifth Avenue, Suite 6300
Seattle, Washington 98104-7092
Phone: (206) 622-4900
Fax: (206) 682-6031

601648_1.DOC